observed event rates for depression and ischaemic heart disease seemed to be higher than expected in a general population.[10] Reframing these observations, however, confirms what clinicians have known for decades: nicotine addiction represents a profound disturbance in brain biology, manifesting as a compulsive disorder with a wide array of predictable consequences. In other words, ischaemic events, depression, and other neuropsychiatric effects might be a function of tobacco dependence and recovery, rather than an effect of the drug choices made during treatment.

Treating tobacco dependence involves a series of personal and professional calculations, sometimes messy and coloured by intense emotions. Against this backdrop, the implications of Kotz and colleagues' study go beyond its obvious points regarding varenicline side-effects. To understand the true relevance of this work requires placing it within historical context, and asking some difficult questions about our own risk-aversive nature. For the past decade, clinicians have been faced with opposing signals from the field. Are adverse events a function of the treatment or the disease? Exactly how safe does a safe medication need to be when weighed against the burden of illness caused by tobacco dependence? Should reliance on anecdotal case reports be allowed when making treatment decisions? How big do observational studies need to be before the guidance they provide can be trusted? Would the answers to these questions be different if the questions weren't about smoking? By providing precise risk estimates associated with the treatment options, Kotz and colleagues' study should allow us to move on comfortably, and begin to examine the nature of our internal calculus of risk with respect to what remains as the single greatest cause of premature death and disability around the world.

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RS has served as a consultant to GlaxoSmithKline and has received free medication (varenicline) and placebo from Pfizer for research purposes. FTL declares no competing interests.

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Elucidating COPD pathogenesis by large-scale genetic analyses

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Chronic obstructive pulmonary disease (COPD) is a heterogeneous syndrome defined by the presence of chronic airflow limitation and associated with other clinical and pathological hallmarks, such as chronic bronchitis, emphysema, exacerbations, and comorbidities. COPD is a complex disease, suggesting that both genetic susceptibility and environmental exposures (eg, cigarette smoking and smoke from biomass fuels) contribute to its pathogenesis (figure). In *The Lancet Respiratory Medicine*, Louise Wain and colleagues[1] report intriguing novel insights into the genetics of smoking behaviour and the airflow obstruction component of COPD.

The genetic study done by the UK Biobank Lung Exome Variant Evaluation (UK BiLEVE) collaborators has many assets.[1] First, big is beautiful in genetics. More than 500 000 individuals have been included in UK Biobank,

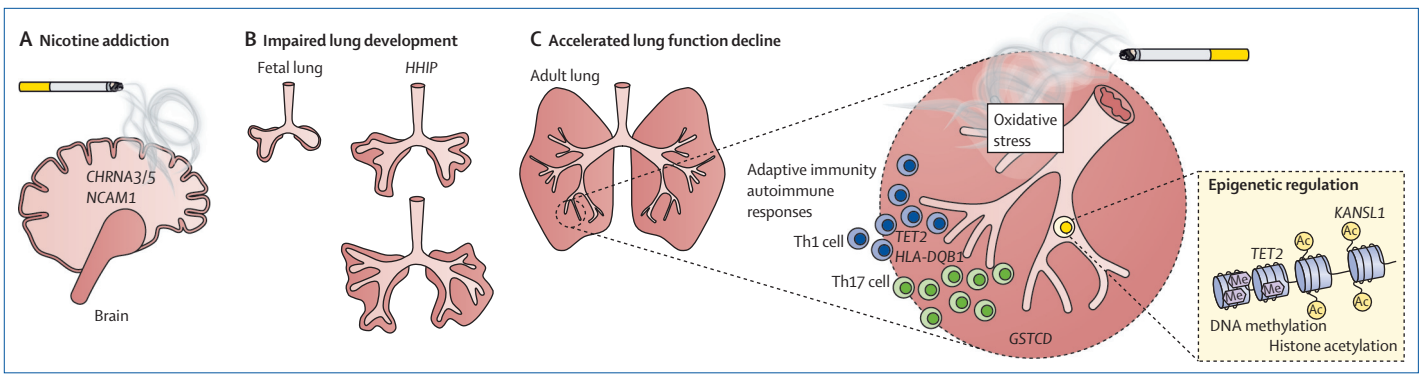

Figure: Genetic susceptibility to chronic obstructive pulmonary disease
Genetic variants contribute to the pathogenesis ofchronic obstructive pulmonary disease through three different pathways: (A) genes expressed in the brain might be involved in nicotine addiction (smoking behaviour); (B) genes expressed in the lungs during fetal life or childhood, or both, might impair lung development and growth in early life; and (C) genes expressed in the lungs might accelerate the decline in lung function in adulthood. Genetic variation in oxidative stress responses, adaptive immunity—including autoimmune responses—and epigenetic regulation (eg, DNA methylation and histone modifications) modulate host responses to cigarette smoke and other air pollutants.

and more than 50 000 individuals of European ancestry were examined in the current study on lung function genetics. Second, the investigators applied a smart sampling strategy, selecting individuals from the middle and extremes of the distribution of lung function (FEV_1) among both never smokers and heavy smokers. Thanks to this nested case-control study design, they enriched the large sample for non-smoking participants with airflow limitation, in whom genetic risk factors are suspected to play a more important part. Third, they used a new custom Affymetrix array to undertake genome-wide genotyping of 807 411 variants, encompassing common (minor allele frequency [MAF] >5%) single nucleotide polymorphisms (SNPs), low-frequency variants (MAF 1–5%), and rare (MAF <1%) coding variants relevant to the UK population. Moreover, by using the 1000 Genomes and UK10K reference panels, this genotyping array provided the unprecedented opportunity to look for association with 28 509 962 genetic variants—imputed or genotyped—in each individual. Multiplying 28·5 million genetic variants by 50 000 participants leads to $1{\cdot}425 \times 10^{12}$ variants analysed—an astronomical number.

What are the main findings? In the genetic association analyses of smoking behaviour, the investigators confirmed the strong association with the nicotinic acetylcholine receptors *CHRNA3* and *CHRNA5* at the 15q25 locus, and discovered five novel regions of association in or near *NCAM1, TEX41/PABPC1P2, DNAH8, NOL4L*, and *LPPR5* (all $p<5 \times 10^{-8}$). For reasons of brevity, we will focus on the *NCAM1* gene, a membrane-bound glycoprotein that mediates adhesion among neurons. Two of the novel signals suggest a functional role for *NCAM1* in nicotine addiction, since one SNP (rs4466874) was located in an intron of *NCAM1* on chromosome 11, and another SNP (rs10193706) located distantly on chromosome 2 modulates the level of expression of *NCAM1* in brain tissue. Moreover, this second SNP is also an expression quantitative trait locus for the gene *WDR61* in the substantia nigra, which plays an important part in reward and addiction.

What insights did the genetic analyses of lung function and COPD provide? Comparing individuals with low FEV_1 with those with high FEV_1, the investigators discovered five novel genetic loci of lung function: *NPNT, TET2, HLA-DQB1/HLA-DQA2, KANSL1, and TSEN54*. The lead SNPs at these loci were more strongly associated with low FEV_1 in never smokers (all $p<5\times10^{-8}$) than in heavy smokers, and were also associated with COPD (defined by spirometry as FEV_1:FVC ratio <0·7 and percent predicted FEV_1<80%). This finding might be surprising, since a low FEV_1 can be caused by airflow obstruction—as in asthma or COPD—or by decreased lung volumes (ie, a restrictive syndrome due to heart failure, interstitial lung disease, or obesity). However, these findings are in line with recent evidence of different trajectories of lung function in the pathogenesis of COPD;[2] about half of the patients have an accelerated decline in lung function, whereas the other half have a normal decline, starting from an already impaired lung function at the age of 20–40 years caused by impaired lung development or growth, or both.[2] The investigators confirmed that the *HHIP* gene, which is involved in fetal lung development and is one of the top hits of the first genome-wide association studies of lung function, is a COPD susceptibility gene.[3]

Several of the newly discovered genes implicate epigenetic regulation in the pathogenesis of COPD. Epigenetic mechanisms modulate the expression of genes by regulating the methylation of DNA or by modifying histones within chromatin. *KANSL1* encodes a key subunit of the histone acetyltransferase complex NSL1. Findings from pharmacological and genetic studies[4,5] have shown roles for histone deacetylases HDAC2 and HDAC4 in the pathogenesis of COPD.[4,5] Since the amount of acetylation of histones within the nucleus determines to what extent specific regions of DNA are accessible to transcription factors, and thus gene activation, these genetic variants might modulate inflammatory responses in the lungs. The gene *TET2* encodes methylcytosine dioxygenase 2, which catalyses the conversion of 5-methylcytosine to 5-hydroxymethylcytosine to mediate DNA methylation. TET2, together with key transcription factors, regulates the differentiation of Th1 and Th17 CD4+ T cells and promotes the expression of interferon-γ and interleukin-17 in these lymphocytes, which suggests that TET2 has a role in autoimmune diseases.[6] Moreover, the association of low FEV_1 with the HLA region on chromosome 6 (HLA-DQB1) also suggests that adaptive immune responses such as Th17 responses might contribute to the development of COPD.[1,7] Although the HLA region has been associated with allergic asthma,[8] the genetic association persisted in individuals without doctor-diagnosed asthma.

What are the next steps? First, the novel genetic associations with lung function and COPD should be replicated in independent cohorts and investigated in people of other ethnic origins. Second, the causative SNPs need to be discovered through fine mapping and the functional role of the putative genes need to be elucidated through translational research approaches. Third, we are looking forward to new genetic studies in UK Biobank that investigate other lung function measurements (eg, FVC and FEV_1:FVC ratio) and other hallmarks of COPD such as chronic bronchitis and emphysema. Thanks to the vast number of participants, the optimum genotyping arrays, and the smart study designs in UK Biobank, the future looks bright for unravelling the genetic cause of COPD.

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We declare no competing interests.

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Towards an integrative genomics of lung function

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Genetic variation is an important determinant of lung function and risk of chronic obstructive pulmonary disease (COPD). Genome-wide association studies (GWAS), first described a decade ago, have become the standard method to study genetic factors influencing these and other complex (non-mendelian) traits and diseases. GWAS can be used to identify novel biological pathways for human disease and ultimately inform diagnostics and therapeutics.[1] However, they have several limitations. One is a lack of power. Although GWAS in most diseases have identified at least a few genetic loci, important insights can only be gained when patterns among many loci are recognised.[2] To detect such patterns, however, large sample sizes are needed, and these can be difficult to achieve. Another major limitation is that GWAS generally implicate regions of the genome rather than specific genes or pathophysiological mechanisms.